Synthesis of C,N,N-Cyclometalated Gold(III) Complexes with Anionic Amide Ligands

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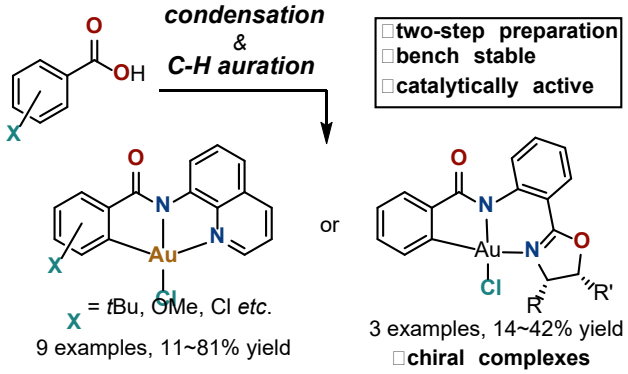
Dedicated to prof Christian Bruneau for his outstanding contribution to catalysis.



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Abstract A series of neutral C,N,N Au(III) complexes was synthesized with *N*-(8-quinolinyl)benzamide derivatives and chiral *N*-(2-(oxazolin-2-yl)phenyl)benzamide derivatives. This convenient synthesis method for amide ligands as well as an operationally simple complexation by direct C-H auration permitted changes to both the steric and electronic properties of the Au(III) complexes for promoting catalytic three-component coupling of an aldehyde, an amine, and an alkyne.

Key words Au(III) complex, amide ligand, pincer complex, catalyst, C-H auration, chiral complex

Homogeneous gold catalysts are of interest due to their unique properties, such as strong π-acidity.[1] Gold catalysts can be classified into two types, Au(I) and Au(III). Catalytically active Au(I) complexes have been developed using various types of ligands, such as phosphines and *N*-heterocyclic carbenes (NHCs).[2] However, application of Au(III) complexes to catalytic reactions has been less explored.[3] This is partly due to the high electrophilicity of Au(III), which leads to instability of the complex and can result in undesirable reductive elimination affording Au(I). For synthesis of stable Au(III) complexes, the use of structurally rigid pincer ligands is an effective approach, leading to suppression of reductive elimination.[4] One reliable synthetic method for stable Au(III) complexes with pincer ligands is a two-step process involving formation of a mercury complex followed by transmetalation to gold (Figure 1a).[5] However, the mercury complex is toxic and dangerous to handle. In contrast, direct complexation between a ligand and Au(III) salt *via* C-H auration is a convenient alternative method (Figure 1b).[6] Nonetheless, derivatization of Au(III) pincer complexes synthesized by the direct C-H auration method is limited partly due to the cumbersome multi-step ligand synthesis process. Since development of a catalytic reaction requires detailed examination of the steric and electronic effects of the catalysts, a novel Au(III) pincer complex that is readily derivatized has been elusive. This report describes the synthesis of novel neutral C,N,N Au(III) complexes *via* direct C-H auration using *N*-(8-quinolinyl)benzamide derivatives as ligands (Figure 1c).[7] Since various *N*-(8-quinolinyl)benzamide derivatives can be synthesized just by condensation of the corresponding carboxylic acids and 8-aminoquinoline, Au(III) complexes could be procured in only two steps from commercially available carboxylic acids. In addition, chiral Au(III) complexes were also synthesized using chiral *N*-(2-(oxazolin-2-yl)phenyl)benzamide derivatives as ligands. The catalytic activities of these Au(III) complexes were demonstrated by three-component coupling of an aldehyde, an amine, and an alkyne (A^3 reaction).[8]

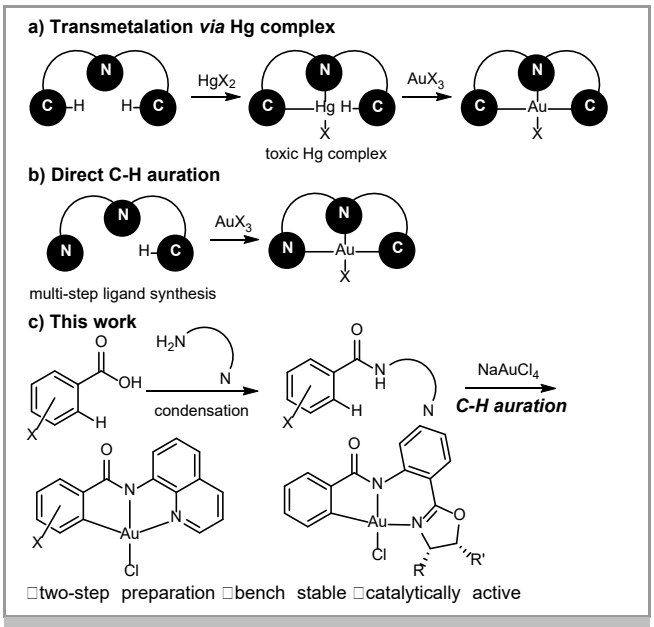
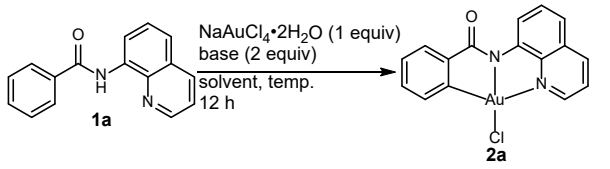


Figure 1. Synthesis of Au(III) pincer complexes.

Complexation reactions using *N*-(8-quinolinyl)benzamide **1a** and $NaAuCl_4 \cdot 2H_2O$ in various solvents at 160 °C were investigated (Table 1, entries 1-3). The C,N,N Au(III) complex **2a** was obtained by reaction in toluene, albeit with concomitant generation of an inseparable byproduct (entry 1, <43% yield). In contrast, **2a** was not produced in DMF (entry 2). Although only a trace amount of **2a** was obtained in MeCN, no contaminating byproduct was detected (entry 3). Addition of water to acetonitrile improved the solubility of $NaAuCl_4 \cdot 2H_2O$, and significantly increases the reactivity (entry 4, 63% yield). However, metallic gold was generated in the reaction mixture. To avoid this, the reaction temperature was reduced to 80 °C, affording **2a** in 53% yield without any sign of metallic gold formation (entry 5). Since protodeauration of **2a** caused by HCl generated *in situ* was suspected, addition of a base was examined. While addition of potassium carbonate completely inhibited the reaction (entry 6), addition of a bulky weak base, potassium pivalate, improved the yield to 65% (entry 7). Compound **2a** was stable and could be stored under air for at least two years.

Table 1. Optimization of Au(III) pincer complex formation.[a]



Entry	Solvent	Temperature (°C)	Base	Yield (%)
1	toluene	160	–	<43
2	DMF	160	–	0
3	CH_3CN	160	–	trace
4	CH_3CN/H_2O 1:1	160	–	63
5	CH_3CN/H_2O 1:1	80	–	53
6	CH_3CN/H_2O 1:1	80	K_2CO_3	0
7	CH_3CN/H_2O 1:1	80	*t*$BuCO_2K$	65

[a] **1a** (0.03 mmol), $NaAuCl_4 \cdot 2H_2O$ (0.03 mmol), solvent (0.025 M), 12 h. Yield of isolated product.

Under optimized reaction conditions, a series of Au(III) complexes were synthesized (Figure 2). When the electron-donating groups, *tert*-butyl and methoxy, were introduced at the *para* position of benzamide, Au(III) complexes **2b** and **2c** were obtained in 81% and 65% yield, respectively. However, an electron-withdrawing chloro substituent inhibited the C-H auration process, producing **2d** in only 11% yield. An *ortho*-methoxy substituent did not affect the reactivity, giving **2e** in 61% yield. When a methoxy group was introduced at the *meta* position, two isomers, **2f** and **2f'**, were obtained in 67% yield in a 4.7:1 ratio. 3,4,5-Trimethoxy substitution also was tolerated to provide **2g** in 69% yield. A π-extended naphthyl derivative provided Au(III) complex **2h** in 64% yield as a single isomer. A complex containing a thiophene group was also obtained in good yield under the same conditions (**2i**, 70% yield).

The C-H auration protocol could be applicable to synthesize chiral Au(III) complexes bearing phenyloxazoline moiety instead of quinoline moiety (Figure 2). Au(III) complexes with isopropyl (**2j**) and benzyl (**2k**) groups on the oxazoline rings were obtained in moderate yield under the same reaction conditions. On the other hand, the ligand with rigid and sterically demanding indanyl group decreased the reactivity to afford **2l** in only 14% yield.

Single crystals of **2a** and **2j** were respectively grown from a $CHCl_3$ solution and CH_2Cl_2/Et_2O solution, and their structures were determined unambiguously by single-crystal X-ray crystallography. Selected bond lengths and angles for **2a** and **2j** are shown in Tables 2 and 3. As expected, both complexes possessed a square planer structure with the four bond angles around the gold atom summing to 360°. The N2-Au-Cl bond angles were almost 180° for both complexes (**2a**: 179°, **2j**: 176°). In sharp contrast, C1-Au-N1 bond of **2a** was slightly nonlinear for **2a** (164°), while the corresponding bond was almost linear for **2j** (173°). The Au-Cl bond lengths were 2.29 Å for both **2a** and **2j**, which is closer to that for a square planar Au(III)-Cl C,N,C pincer complex with a pyridine group at the *trans* position(2.28 Å)[9] than that for a C,C,N pincer complex with a C(sp^2) anion ligand at the *trans* position (2.37 Å).[10]

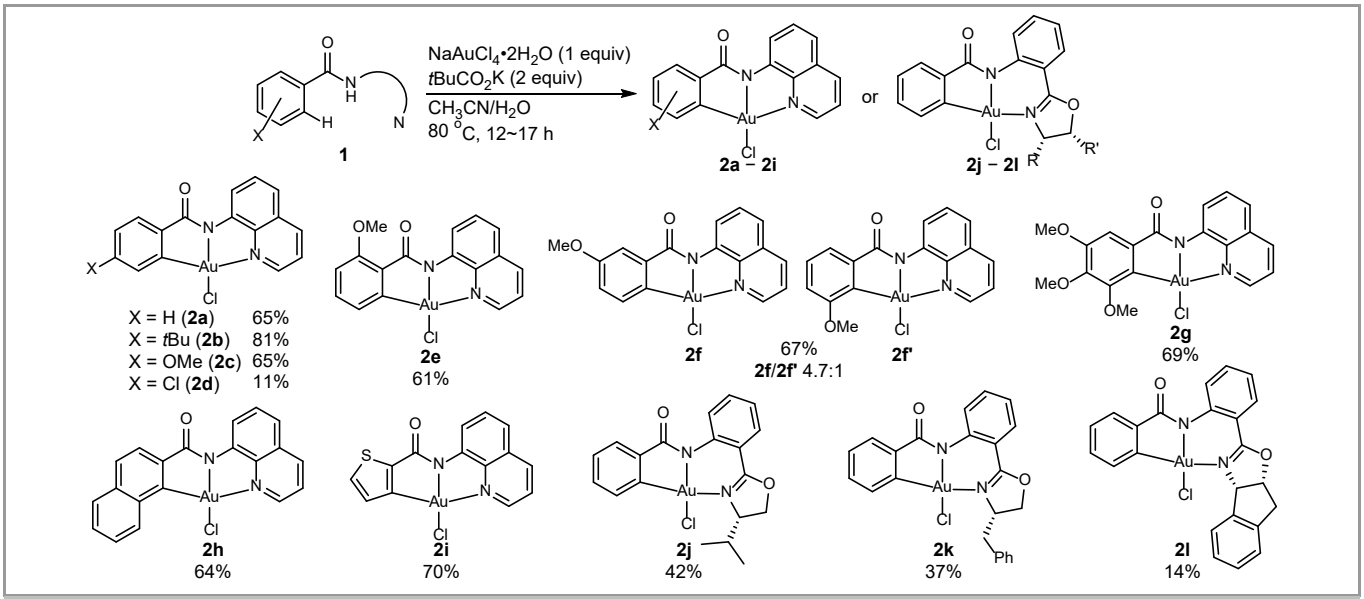
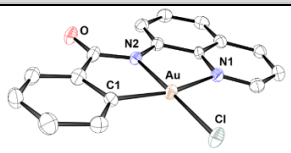


Figure 2. Substrate scope: **1** (0.1 mmol), $NaAuCl_4 \cdot 2H_2O$ (0.1 mmol), CH_3CN/H_2O (1:1, 0.025 M), 12~17 h. Yield of the isolated product.

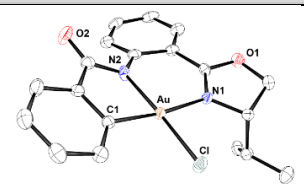
Table 2. Selected bond lengths (Å) and angles (deg) for **2a**.[a]



Au-Cl	2.2906(14) Å	N1-Au-N2	81.64(19) deg
Au-N1	2.114(5) Å	C1-Au-N2	82.3(2) deg
Au-N2	1.984(5) Å	C1-Au-Cl	96.97(17) deg
Au-C1	2.011(6) Å	N1-Au-Cl	99.13(14) deg
N2-Au-Cl	178.97(15) deg	C1-Au-N1	163.9(2) deg

[a]ORTEP drawing of **2a** showing 50% probability thermal ellipsoids. All hydrogen atoms were omitted for clarity.

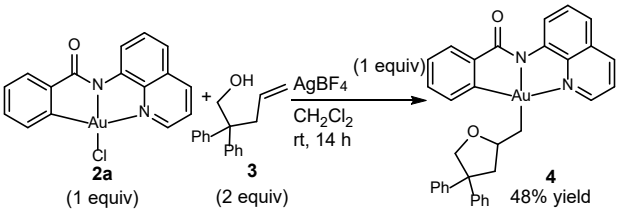
Table 3. Selected bond lengths (Å) and angles (deg) for **2j**.[a]



Au-Cl	2.289(2) Å	N1-Au-N2	92.4(2) deg
Au-N1	2.078(6) Å	C1-Au-N2	83.0(3) deg
Au-N2	1.997(6) Å	C1-Au-Cl	92.5(2) deg
Au-C1	2.007(7) Å	N1-Au-Cl	92.02(18) deg
N2-Au-Cl	175.53(17) deg	C1-Au-N1	173.1(3) deg

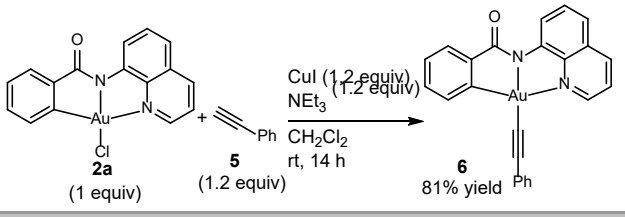
[a]ORTEP drawing of **2j** showing 50% probability thermal ellipsoids. All hydrogen atoms were omitted for clarity.

Next, the reactivity of the Au(III) complex **2a** was examined. When the hydroxy alkene **3** and **2a** were treated by 1 equivalent of $AgBF_4$, oxyauration of the C-C double bond proceeded and alkyl Au(III) complex **4** was obtained in 48% yield (Scheme 1). A cationic gold complex, generated *in situ* by abstracting chloride anions with Ag salt, worked as a π-acid to induce cyclization. As expected, alkyl Au(III) complex **4** did not undergo reductive elimination and was stable under air.



Scheme 1. Oxyauration of hydroxyalkene **3**.

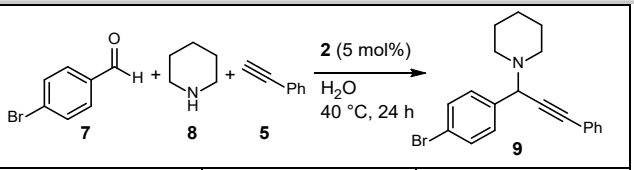
Synthesis of alkynyl Au(III) complex **6** was also successful (Scheme 2). Although the target product could not be obtained by addition of lithium alkynide, **6** was obtained using a copper alkynide generated *in situ* as a nucleophile.



Scheme 2. Synthesis of alkynyl Au(III) complex.

Since the alkynyl Au(III) **6** could be obtained, Au(III) complex **2** was used as a catalyst for three-component coupling of an aldehyde, amine, and alkyne, (*i.e.*, A^3 reaction), in which the alkynylgold was the active nucleophile.[8] When 5 mol% $AuCl_3$ was applied to the coupling of 4-bromobenzaldehyde, piperidine, and phenylacetylene in water at 40 °C, the product was obtained in 69% yield (Table 4, entry 1). The reaction using Au(III) complex **2a** significantly decreased the yield to 27% (entry 2). Moderate yields were obtained with complexes containing electron-donating substituents, such as *tert*-butyl (**2b**) and methoxy (**2c**) groups, at the C5 position (entry 3, 65% yield; entry 4, 50% yield). In contrast, having an electron-withdrawing 5-chloro substituent (**2d**) decreased the yield (entry 5, 19% yield). A 3-methoxy substituent (**2e**) further improved the yield to 74% (entry 6), while 4,5,6-trimethoxy substitution (**2g**) did not have a positive effect (entry 7, 22% yield). The highest catalytic activity was observed with **2h** containing a sterically demanding naphthyl group to give the product in 85% yield (entry 8, 73% isolated yield). The thiophene-containing complex **2i** also was effective, albeit with moderate activity (entry 9, 63% yield). Chiral Au(III) complexes were also examined for the A^3 reaction (entries 10-12). All the complexes showed moderate catalytic activities (**2j**: 57% yield, **2k**: 39% yield, **2l**: 54% yield (50% isolated yield)), while no enantioinduction was observed. When the catalyst loading was lowered to 0.5 mol% with the most reactive complex **2h** (entry 13), the yield of the product decreased to 32% despite the prolonged reaction time (51 h). Although the catalytic activities of the tested Au(III) complexes are not high enough compared to the precedented high-performance Au(III) catalysts,[8c] the results clearly indicate that optimizing various parameters for the C,N,N Au(III) complexes, including electronic and steric factors, could improve catalytic activity.

Table 4. Investigation of A^3 reaction using **2**.[a]



Entry	Complex	Yield (%)
1	$AuCl_3$	69
2	**2a**	27
3	**2b**	65
4	**2c**	50
5	**2d**	19
6	**2e**	74
7	**2g**	22
8	**2h**	85 (73)
9	**2i**	63
10	**2j**	57
11	**2k**	39
12	**2l**	54 (50)
13[b]	**2h**	32

[a]**7** (0.1 mmol), **8** (0.11 mmol), **5** (0.15 mmol), **2** (0.005 mmol), H_2O (0.5 M), 40 °C, 24 h. Yields were determined by ^1H NMR analysis using tetrachloroethane as an internal standard. Yield of the isolated product is shown in parentheses. [b] 0.5 mol% of **2h** (0.0005 mmol) was used and the reaction time was 51 h.

In conclusion, novel pincer-type C,N,N neutral Au(III) complexes were developed. A convenient ligand synthesis, involving condensation of carboxylic acids with 8-aminoquinoline, produced a series of Au(III) complexes with

various steric and electronic properties. Moreover, chiral Au(III) complexes were also prepared using *N*-(2-(oxazolin-2-yl)phenyl)benzamide derivatives. Oxyauration of the hydroxy alkene **3** by **2a** in the presence of $AgBF_4$ demonstrated π-acidity of the cationic Au(III) complex generated *in situ*. In addition, investigation of a catalytic A^3 reaction using **2** clearly showed that substituents on the benzamide moiety could affect the catalytic activity of the complex. Further exploration of catalytic reactions including asymmetric reactions with the Au(III) complexes is ongoing.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(11) **General procedure for the synthesis of Au(III) complex 2**

To a sealed tube, **1** (0.1 mmol), $NaAuCl_4{\cdot}2H_2O$ (39.8 mg, 0.1 mmol), potassium pivalate (19.6 mg, 0.2 mmol), CH_3CN (2 mL) and H_2O (2 mL) were added. The mixture was stirred overnight at 80 °C and then cooled to room temperature. The precipitate was filtered and washed with methanol and dry *in vacuo* to give **2** as a yellowish brown solid.

Characterization data of 2a

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.14 (d, *J* = 5.2 Hz, 1H), 9.03 (d, *J* = 7.6 Hz, 1 H), 8.48 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H), 7.65-7.71 (m, 2H), 7.54 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.34 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1 H), 7.29 (dd, *J* = 1.6, 8.0 Hz, 1 H);^{13}C NMR (100.5 MHz, $CDCl_3$): δ 174.53, 146.56, 144.90, 144.02, 142.18, 141.19, 139.31, 132.42, 131.04, 130.76, 130.67, 130.41, 128.85, 121.91, 121.41, 120.91; IR (ATR): 2945, 1647, 1625, 1579, 1504, 1463, 1400, 1381 cm^{-1}; HRMS (FD): m/z calcd for $C_{16}H_{10}AuClN_2O$ $[M]^+$ 478.0147, found 478.0129.

Alkyl Au(III) complex (4).

In a glove box, **2a** (47.9 mg, 0.1 mmol), 2,2-diphenylpent-4-en-1-ol **3** (47.7 mg, 0.2 mmol), $AgBF_4$ (19.5 mg, 0.1 mmol) and DCM (1 mL) were added to a vial equipped with a magnetic stirring bar. The mixture was stirred for 14 h at room temperature. Solvent was removed under reduced pressure. The crude material was purified by silica gel flash chromatography using gradient elution (starting with hexane to hexane/EtOAC 9/1) to give 31.1 mg of **4** (65% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.61 (dd, *J* = 1.6, 5.2 Hz, 1H), 8.40 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.71-7.75 (m, 1H), 7.65 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.52 (dd, *J* = 5.2, 8.4 Hz, 1H), 7.36-7.40 (m, 2H), 7.28-7.32 (m, 2H), 7.20-7.28 (m, 9H), 7.12-7.19 (m, 1H), 4.59 (ddt, *J* = 6.4, 6.8, 8.0 Hz, 1H), 4.44 (d, *J* = 8.8 Hz, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 2.88 (dd, *J* = 6.8, 12.4 Hz, 1H), 2.59 (dd, *J* = 8.0, 12.4 Hz, 1H), 2.00 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.39, 146.51, 146.46, 146.08, 144.72, 140.57, 135.52, 131.33, 130.60, 129.95, 128.95, 128.41, 128.37, 127.63, 127.26, 127.07, 126.36, 126.25, 121.42, 121.14, 119.51, 80.28, 56.58, 47.57, 34.88; IR (ATR): 2972, 1625, 1582, 1502, 1466, 1394 cm^{-1}; HRMS (ESI): m/z calcd for $C_{33}H_{28}AuN_2O_2$ $[M+H]^+$ 681.1811, found 681.1827.

Alkynyl Au(III) complex (6)

In a glove box, **2a** (47.9 mg, 0.1 mmol), phenylacetylene **5** (12.3 mg, 0.12 mmol), CuI (22.9 mg, 0.12 mmol), NEt_3 (12.1 mg, 0.12 mmol) and DCM (1 mL) were added to a vial equipped with a magnetic stirring bar. The mixture was stirred for 14 h at room temperature. Solvent was removed under reduced pressure. The crude material was purified by silica gel flash chromatography using gradient elution (starting with hexane to hexane/EtOAC 9/1) to give 43.8 mg of **6** (81% yield) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24 (dd, *J* = 1.2, 4.8 Hz, 1H), 9.02 (dd, *J* = 1.6, 8.4 Hz, 1H), 8.50 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.94 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.65-7.72 (m, 2H), 7.59-7.64 (m, 3H), 7.49 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.26-7.40 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 174.94, 148.32, 146.40, 145.12, 144.47, 140.95, 136.20, 133.78, 132.28, 131.84, 131.26, 130.77, 130.04, 128.30, 128.23, 127.51, 125.35, 121.92, 121.70, 120.35, 97.94, 96.44; IR (ATR): 3053, 2989, 1640, 1594, 1582, 1501, 1487, 1462, 1450, 1441, 1384 cm^{-1}; HRMS (ESI): m/z calcd for $C_{24}H_{16}AuN_2O$ $[M+H]^+$ 545.0923, found 545.0937.

General procedure for A^3 reaction

Compound **2** (0.005 mmol), 4-bromo benzaldehyde **7** (18.5 mg, 0.1 mmol), piperidine **8** (9.4 mg, 0.11 mmol) and phenylacetylene **5** (15.3 mg, 0.15 mmol) were added to a vial equipped with a magnetic stirring bar. Then, H_2O (0.2 mL) was added to the mixture. The resulting suspension was stirred for 24 h at 40 °C and then cooled to room temperature. The mixture was extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$. The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard.